Citation:

Buijsse B, Feskens EJM, Kok FJ, Kromhout D. Cocoa intake, blood pressure and cardiovascular mortality: the Zutphen Elderly Study. *Arch Intern Med.* 2006; 166 (4): 411-417.

PubMed ID: 16505260

Study Design:

Cohort study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To study whether habitual cocoa intake was inversely related to blood pressure and cardiovascular mortality in elderly men living in Zutphen, the Netherlands.

Inclusion Criteria:

Elderly men, aged 65 to 84 years, participating in the Zutphen Elderly Study and free of chronic disease at baseline.

Exclusion Criteria:

Subjects without estimation of dietary intake, information on risk factors and chronic disease prevalence, history of CVDs, diabetes mellitus or cancer at baseline or those who were taking an antihypertensive medication.

Description of Study Protocol:

- *Recruitment:* Elderly men participating in the Zutphen Elderly Study, a continuation of the Zutphen Study, the Dutch contribution to the Seven Countries Study
- *Design:* Cohort study
- *Intervention:* Subjects completed questionnaires, dietary interviews, blood pressure and blood samples.

Statistical Analysis

- Random intercept model was used to calculate adjusted means and 95% confidence intervals of blood pressure for each tertile of cocoa intake
- In addition to an age-adjusted model, three multiple regression models were used to adjust for other factors associated with cocoa intake and well-known determinants of blood pressure
- Dietary covariates adjusted for total calorie intake according to the residual method
- Relative risks and 95% confidence intervals for the association between cocoa intake and cardiovascular and all-cause mortality were estimated using Cox proportional hazards models, in which the middle and highest tertiles of cocoa intake were compared with the

lowest tertile
- Adjustment for continuous distributed covariates was done time-independently: For discrete variables, we used baseline data
- Stratified analyses were performed for major cardiovascular risk factors
- All statistical tests were two-sided.

Data Collection Summary:

Timing of Measurements

- Baseline measurements made in 1985 and repeated examinations were made in 1990 and 1995
- Blood pressure was measured at baseline and five years later
- Causes of death ascertained during 15 years of follow-up
- Habitual food consumption assessed by cross-check dietary history method in 1985, 1990 and 1995.

Dependent Variables

- Blood pressure measured twice at end of physical exam using random-zero sphygmomanometer
- Causes of death checked through municipal registries and hospital discharge data
- Weight, height and BMI
- Serum samples tested for total and HDL cholesterol, serum homocysteine
- Medical history of myocardial infarction, angina pectoris, intermittent claudication, heart failure, diabetes mellitus, cancer with standardized questionnaire.

Independent Variables

- Habitual food consumption estimated in 1985, 1990 and 1995 by dietitians through cross-check dietary history
- Cocoa intake was estimated from the consumption of cocoa-containing foods
- All subjects interviewed at home for one hour in the presence of person preparing meals
- Intake calculated using Netherlands Food Composition Tables
- 24 cocoa-containing foods reported by subjects and consumption of these foods was multiplied by cocoa content
- Reproducibility of dietary history tested three and 12 months after study start; baseline cocoa intake correlated with cocoa intake at five and 10 years. Spearman R=0.45 and R=0.43, respectively; $P<0.001$ for both.

Control Variables

- Physical acitivity estimated using validated questionnaire designed for retired men
- Questionnaire used to collect data on cigarette smoking, socioeconomic status and use of hypertensive drugs, aspirin and anticoagulants.

Description of Actual Data Sample:

Initial N

- 367 of 555 men in the original cohort, who were still alive participated. In addition, a random sample of 711 other men of the same age and also living in Zutphen were selected. In total, 1,266 men were invited, 939 (74.2%) participated in the study.
- In 876 men, dietary intake was estimated. Information on risk factors and chronic disease prevalence available for 790 men
- 320 excluded based on exclusion criteria.

Attrition (Final N)

470 elderly men.

Age

Aged 65 to 84 years.

Ethnicity

Not mentioned.

Location

The Netherlands.

Summary of Results:

Blood Pressure	Lowest Tertile (<0.36g per Day)	Middle Tertile (0.36-2.30g per Day)	Highest Tertile (>2.30g per Day)	P-Value for Trend
SBP - Crude	149.7 (147.3-152.2)	148.8 (146.5-151.1)	147.0 (144.6-149.5)	0.08
SBP - Age adjusted	149.6 (147.2-152.0)	148.8 (146.4-151.1)	147.0 (144.6-149.5)	0.09
SBP - Model A	149.9 (147.4-152.4)	148.9 (146.6-151.2)	146.9 (144.4-149.4)	0.07
SBP - Model B	150.2 (147.7-152.8)	149.0 (146.7-151.3)	146.5 (144.0-149.1)	0.03
SBP - Model C	150.0 (147.5-152.6)	148.8 (146.5-151.2)	146.9 (144.4-149.4)	0.06
DBP - Crude	84.4 (82.9-85.8)	83.6 (82.3-85.0)	82.2 (80.8-83.6)	0.02
DBP - Age adjusted	84.5 (83.1-85.9)	83.7 (82.3-85.0)	82.2 (80.8-83.6)	0.01
DBP - Model A	84.2 (82.8-85.6)	83.8 (82.5-85.1)	82.5 (81.1-83.8)	0.05
DBP - Model B	84.4 (83.0-85.8)	83.8 (82.5-85.1)	82.3 (80.9-83.7)	0.03

DBP - Model C	84.3 (82.9-85.7)	83.8 (82.5-83.7)	82.3 (80.9-83.7)	0.03

Other Findings

- One-third of the men did not use cocoa in 1985 at baseline. The median cocoa intake among users was 2.11g per day in 1985, 2.30g per day in 1990 and 2.36g per day in 1995.
- After multivariate adjustment, the mean systolic blood pressure in the highest tertile of cocoa intake was 3.7mm Hg lower (95% confidence interval: -7.1 to -0.3mm Hg, P=0.03 for trend) and the mean diastolic blood pressure was 2.1mm Hg lower (95% confidence interval: -4.0 to -0.2mm Hg, P=0.03 for trend), compared with the lowest tertile
- During follow-up, 314 men died (66.8%), 152 of cardiovascular diseases
- Compared with the lowest tertile of cocoa intake, the adjusted relative risk for men in the highest tertile was 0.50 (95% confidence interval: 0.32 to 0.78, P=0.004 for trend) for cardiovascular mortality and 0.53 (95% confidence interval: 0.39 to 0.72, P<0.001) for all-cause mortality.

Author Conclusion:

- In a cohort of elderly men, cocoa intake is inversely related with blood pressure and 15-year cardiovascular and all-cause mortality
- In conclusion, to our knowledge this is the first observational study that found habitual cocoa intake was inversely associated with blood pressure in cross-sectional analysis and with cardiovascular and all-cause mortality in prospective analysis
- Before drawing conclusions, confirmation by other observational and experimental studies is needed.

Reviewer Comments:

- *Reproducibility of dietary history was tested*
- *Well-defined inclusion and exclusion criteria.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes

4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	Yes
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	N/A
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	N/A
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	N/A
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	Yes
6.6.	Were extra or unplanned treatments described?	Yes
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes

7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes